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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Gregory A. Kopia et. al.  
Serial No.: 09/575,480 Art Unit: 3743  
Filed : May 19, 2000 Examiner: C.T. Nguyen  
For : DRUG COMBINATIONS USEFUL FOR PREVENTION OF  
RESTENOSIS

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November 29, 2005

(Date)

Paul A. Coletti

Name of applicant, assignee, or Registered Representative

/Paul A. Coletti/

(Signature)

November 29, 2005

(Date of Signature)

AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT

Mail Stop Appeal Brief-Patents  
Commissioner for Patents  
P.O. Box 1450  
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Dear Sir:

Attached is the second corrected Appeal Brief for the above-captioned patent application.

Please charge Deposit Account No. 10-0750/CRD0850/PAC in the name of Johnson & Johnson in the amount of \$500.00, representing the cost of filing a Brief on Appeal in the above-captioned matter.

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Respectfully submitted,

/Paul A. Coletti/

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Applicants: Gregory A. Kopia et. al.

Serial No.: 09/575,480

Art Unit: 3743

Filed : May 19, 2000

Examiner: C.T. Nguyen

For : DRUG COMBINATIONS USEFUL FOR PREVENTION OF RESTENOSIS

**APPELLANT'S SECOND CORRECTED BRIEF ON APPEAL**

Mail Stop Appeal Brief-Patents  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

The following represents Appellant's Brief on Appeal in the above-captioned application:

**I. REAL PARTY IN INTEREST**

The real party of interest of the present application on appeal is the assignee, Cordis Corporation.

**II. RELATED APPEALS AND INTERFERENCES**

There are no appeals or interferences known to appellant's legal representative or assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**III. STATUS OF CLAIMS**

Claims 1, 3 – 4, 6, and 8 – 9 are pending in this application and have been finally rejected in this application by means of a final rejection dated June 2, 2004. Claims 2, 5, 7, and 10 – 15 were cancelled without prejudice during prosecution. Each of Claims 1, 3 – 4, 6, and 8 – 9 are on appeal.

#### **IV. STATUS OF AMENDMENTS**

A Response after Final Rejection was deposited with the United States Postal Service on September 2, 2004 in response to the Final Rejection dated June 2, 2004. In an Advisory Action mailed on October 19, 2004, the Examiner indicated that the Response after Final Rejection failed to place the application in condition for allowance. Nonetheless, the Examiner entered the claim amendments made in the Response after Final Rejection.

#### **V. SUMMARY OF CLAIMED SUBJECT MATTER**

The invention embodied by the subject application on appeal is directed to an approach to solving the clinical problem of restenosis, which involves the administration of drug combinations, either locally or systemically. One example of such a combination would be the addition of the anti-inflammatory corticosteroid, dexamethasone, with an antiproliferative agent such as rapamycin or its analogues. Delivery of a stent containing both an *antiproliferative agent and an anti-inflammatory agent (emphasis added)* to a coronary artery injured during the process of angioplasty would provide the added therapeutic benefit of:

1. Limiting the degree of local smooth muscle cell proliferation;
2. Reducing a stimulus for proliferation, i.e., inflammation, and thus enhance the restenosis-limiting action of the stent.

An additional benefit of combination drug therapy may be to reduce the dose of each of the therapeutic components and thus limiting their toxicity, while still achieving a reduction in restenosis. See Table 1 (included below), which demonstrates that concentrations of rapamycin or dexamethasone below their respective IC<sub>50</sub> amounts may combine to produce an effect on cell growth greater than either agent individually.

% of Control Growth	Concentration of Dexamethasone									
	0	0.01	0.05	0.1	0.5	1.0	5.0	10	50	100
Rapamycin 0 ug/ml	100.0	-	-	75.2	76.5	72.2	50.0	36.1	18.3	11.7
Standard Deviation	4.2			0.8	16.3	9.3	7.6	5.9	6.0	1.3
Rapamycin 0.2 ug/ml	85.7	63.4	57.6	49.7	48.9	48.2	41.2	31.1	31.2	29.0
Standard Deviation	6.6	3.2	2.1	4.6	2.2	1.7	3.0	2.7	1.0	1.8
Rapamycin 1.0 ug/ml	67.4	48.3	45.1	38.1	39.2	37.8	33.9	25.8	20.7	18.5
Standard Deviation	2.6	3.3	13.3	9.5	4.4	4.5	3.1	8.1	6.4	3.7

Table 1: Inhibition of human vascular smooth muscle cell proliferation with dexamethasone or dexamethasone + rapamycin.

Further aspects of this summary are seen in the specification at page 8, lines 7-23, page 10, lines 14-28, page 11, lines 11-15, and page 13, lines 11-20.

## **VI. GROUNDS OF PROTECTION TO BE REVIEWED ON APPEAL**

1. Is Claim 1 patentable in light of 35 U.S.C. §112?
2. Are Claims 1, 3, 4, and 6 patentable under 35 U.S.C. §102 in view of U.S. Patent No. 6,335,029 to Kamath?
3. Are Claims 8-9 patentable under 35 U.S.C. §103 over U.S. Patent No. 6,335,029 to Kamath in view of U.S. Patent No. 6,159,488 to Nagler?
4. How can Applicants overcome the double patenting rejection?

## **VII. ARGUMENT**

1. *Is Claim 1 patentable in light of 35 U.S.C. §112?*

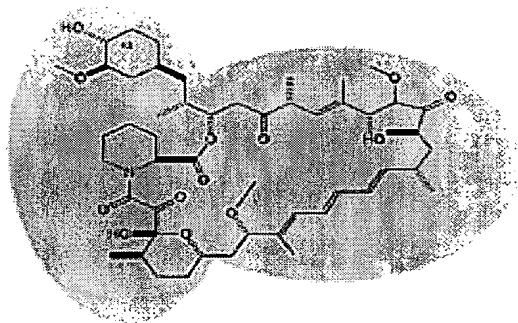
Claim 1 is patentable in light of 35 U.S.C. §112. As amended, claim 1 now satisfies all of the requirements 35 U.S.C. §112. The Examiner originally rejected claim 1 under 35 U.S.C. §112 for lack of antecedent basis for the term “said layers.” As noted in applicant’s response dated September 2, 2004, an inadvertent typographical error inserted the word “layers” for the word “agents.” The term “said agents” now has antecedent support in amended claim 1, thus making the claim reasonably ascertainable by those skilled in the art. [*Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992)]

2. *Are Claims 1, 3, 4, and 6 patentable under 35 U.S.C. §102 in view of U.S. Patent No. 6,335,029 to Kamath?*

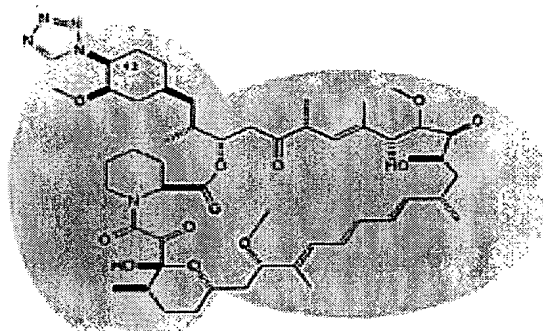
Claims 1, 3, 4, and 6 are patentable under 35 U.S.C. §102 over U.S. Patent No. 6,335,029 to Kamath, et. al. The Examiner has rejected Claim 1 under 35 U.S.C. §102, citing Kamath. In so doing, the Examiner has characterized the drug Taxol as a rapamycin “analogue.” Applicants respectfully contend that this is an improper characterization.

Taxol is formed from the compound paclitaxel. While both rapamycin and paclitaxel may exhibit antiproliferative properties, these two drugs are different in both their chemical structure and method of action. The attached drawings show the chemical structure of both rapamycin and paclitaxel. Upon a review of the images, one can see clearly that the chemical structures of these compounds share little in common. In this regard, one could not characterize the two families of drugs as “analogues.” In contrast, each pair of the true “analogues” (for instance, rapamycin and its analogue, ABT-578, or taxol and its analogue, docetaxel) has very similar structures. As well, both pairs of true analogues have similar methods of action.

Chemical Structure - Rapamycin and a Rapamycin Analogue:

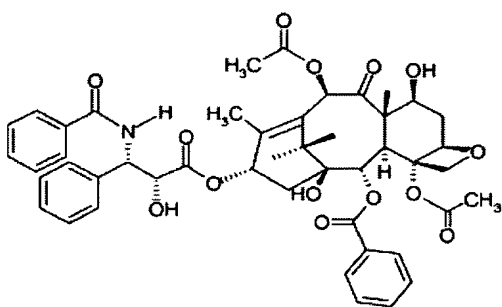


**Rapamycin**

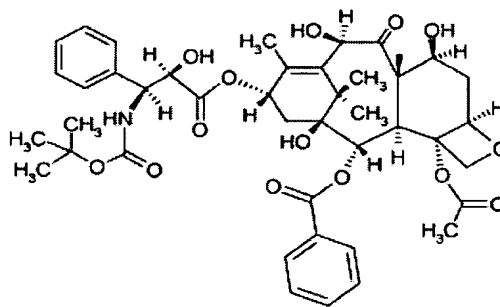


**ABT-578 (A Rapamycin Analogue)**

Chemical Structure - Taxol and a Taxol Analogue:



**Paclitaxel (Taxol)**



**Docetaxel (A Paclitaxel Analogue)**

The method of action of these two classes of drugs is quite different. Paclitaxel is a drug originally formulated for cancer therapy, since it interferes with the growth of cancer cells, which are eventually destroyed. Essentially, paclitaxel causes cells to experience programmed cell death without dividing. Rapamycin, also known as sirolimus was formulated as an immunosuppressive agents to prevent tissue rejection during transplant surgery. Sirolimus works to prevent the white blood cells from getting rid of the transplanted organ, and in so doing exhibits cytostatic properties.

The Examiner's argument is misplaced that, because applicant originally submitted claims pairing rapamycin with taxol and vincristine in a *Markush* grouping<sup>1</sup>, the agents cited are "analogues." A *Markush* grouping is a homegrown generic expression covering a group of two or more different materials, any one of which will be operative for the combination claimed. Applicant submits that, to extrapolate that the elements of a *Markush* grouping, are

<sup>1</sup> See Claim 9.

necessarily *analogues* as used in the drug sense, is entirely inappropriate. Moreover, without a clear showing made by the Examiner that the drugs function as analogues, any argument based on inherency of the drugs' properties is certainly inappropriate, given appellants clear showing of the different modes of operation.

Examiner makes the additional argument that the dictionary meaning of "analogue" is defined as a structure that is similar in function to one in another according to The American Heritage® Dictionary. However, the pharmaceutical sense, "analogue" has a more specific meaning specifically, "a chemical compound with a structure similar to that of another but differing from it in respect to a certain component."<sup>2</sup> Under this definition, clearly taxol is not a rapamycin "analogue."

Since appellants have shown that taxol is not a rapamycin analogue, and Kamath does not disclose a rapamycin or a rapamycin analogue, the rejection in light of Kamath is inappropriate.

*3. Are Claims 8-9 patentable under 35 U.S.C. §103 over U.S. Patent No. 6,335,029 to Kamath in view of U.S. Patent No. 6,159,488 to Nagler?*

Claims 8 and 9 are patentable under 35 U.S.C. §103 over Kamath in view of U.S. Patent No. 6,159,488 to Nagler, et al. It has already been shown herein that taxol is not a rapamycin analogue. In this regard, Kamath in view of Nagler does not teach or suggest each of the claim limitations, specifically the use of an antiproliferative "comprising rapamycin or an analogue thereof..."

The examiner states that the Kamath reference discloses the invention as applied to Claim 1 but fails to recite halofuginone as an extracellular matrix inhibitor. The examiner further cites the Nagler reference to teach a stent coated with halofuginone, and then states it would be obvious to one with ordinary skill in the art to modify Kamath to include halofuginone. "When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine said references." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed Cir. 1998). There is no such suggestion or motivation in either reference to combine the cited references. The Examiner has shown no suggestion or motivation to combine, and the references themselves do not imply a reason to combine these references. Furthermore, Kamath simply *does not teach* the use of an antiproliferative comprising rapamycin or an analogue thereof.

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<sup>2</sup> Dorland's Medical Dictionary, pg. 66 (26<sup>th</sup> ed. 1981).

Given that Kamath falls short as a 35 USC §102 reference as it relates to the claimed invention, it also falls short as a 35 USC §103 reference as applied herein. In this regard, claims 8 and 9 are patentable under 35 U.S.C. §103.

*4. How can Applicants overcome the double patenting rejection?*

Applicants expect the double patenting rejection to be removed in light of the further prosecution of S.N. 09/850,482.<sup>3</sup> Alternately, if the double patenting rejection is maintained, Applicants intend to file a Terminal Disclaimer to overcome such rejection.

**SUMMARY**

Appellants submit that the above remarks and supporting information establish that the Examiner's cited grounds for rejection are improper and as such should be reversed. Appellant thus respectfully requests that the Board of Patent Appeals and Interferences find that the remaining claims are in condition for allowance, with instructions to the Examiner to allow the claims.

Respectfully submitted,

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<sup>3</sup> For instance, in S.N. 09/850,482 only claims 1-3 and 5-15 remain, not 1-20 and 25 as cited by the Examiner.

## **APPENDIX**

### **VIII. CLAIMS**

1. (Previously Amended) A method for treating restenosis comprising an intravascular infusion or delivery by release from a surface of a stent of a combination of at least two agents, including an anti-proliferative agent for inhibiting smooth muscle cell growth comprising rapamycin or an analogue thereof and an anti-inflammatory agent for inhibiting smooth muscle growth, both said agents contained in therapeutic dosage amounts.
2. (Canceled)
3. (Previously Amended) The method of claim 1 wherein the anti-inflammatory agent comprises dexamethasone.
4. (Previously Amended) The method of claim 1 wherein the combination of at least two agents further includes a growth factor or cytokine signal transduction inhibitor.
5. (Canceled)
6. (Previously Amended) The method of claim 1 wherein the combination of at least two agents further includes a tyrosine kinase inhibitor.
7. (Canceled)
8. (Previously Amended) The method of claim 1 wherein the combination of at least two agents further includes an inhibitor of extracellular matrix synthesis.
9. (Previously Amended) The method of claim 8 wherein the inhibitor of extracellular matrix synthesis comprises halofuginone and the anti-proliferative agent is taken from a group consisting of rapamycin, taxol, or vincristine.
10. (Canceled)
11. (Canceled)
12. (Canceled)



13. (Canceled)

14. (Canceled)

15. (Canceled)

**IX. EVIDENCE APPENDIX**

Copies of Kamath, U.S. Patent No. 6,335,029 and Nagler, U.S. Patent 6,159,488.

**X. RELATED PROCEEDINGS APPENDIX**

None

DORLAND'S ILLUSTRATED

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# Medical Dictionary

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Twenty-sixth Edition

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**anal** (a'nal) [L. *analis*] pertaining to the anus.

**analbuminemia** (an'al-bu'mi-ne'me-ah) a state characterized by deficiency or absence of albumins in the blood serum.

**analeptic** (an'ah-lep'tik) [Gr. *analepsis* a repairing] a drug which acts as a restorative, such as caffeine, amphetamine, pentylenetetrazol, etc.

**analgesia** (an'al-je'ze-ah) [an neg. + Gr. *algēsis* pain + *-ia*] absence of sensibility to pain; absence of pain on noxious stimulation; designating particularly the relief of pain without loss of consciousness; called also *alganesthesia*. **a. al'gera**, spontaneous pain in a denervated part; pain in an area or region which is anesthetic; called also *a. dolorosa*. **audio a.**, audioanalgesia, continuous caudal a., the relief of the pain of labor and childbirth by the continuous bathing of the sacral and lumbar plexuses within the epidural space by the injection of an anesthetic solution. This method is used also in general surgery to block the pain pathways below the navel. Called also *continuous caudal anesthesia*. **a. dolorosa**, *a. algera*. **epidural a.**, analgesia induced by introduction of the analgesic agent into the epidural space of the vertebral canal. **infiltration a.**, paralysis of the nerve endings at the site of operation by subcutaneous injection of an anesthetic. **narcoclocal a.**, local analgesia preceded by premedication. **paretic a.**, loss of the sense of pain accompanied by partial paralysis. **permeation a.**, surface a. **relative a.**, in dental anesthesia, a maintained level of consciousness-sedation, short of general anesthesia, in which the pain threshold is elevated, usually induced in inhalation of nitrous oxide and oxygen. **surface a.**, local analgesia produced by an anesthetic applied to the surface of such mucous membranes as those of the eye, nose, throat, larynx, and urethra; called also *permeation a.*

**analgesic** (an'al-je'zik) 1. relieving pain. 2. not sensitive as to pain. 3. an agent that alleviates pain without causing loss of consciousness.

**Analgesine** (an'al-je'sin) trademark for a preparation of antipyrine.

**analgetic** (an'al-jet'ik) analgesic.

**analgia** (an'al-je-ah) [an neg. + Gr. *algos* pain + *-ia*] absence of pain.

**analgetic** (an'al-jik) insensible to pain.

**anallergic** (an'ah-ler'jik) not allergic; not causing anaphylaxis or hypersensitivity.

**analogous** (ah-nal'o-gus) [Gr. *analogos* according to a due ratio, conformable, proportionate] resembling or similar in some respects, as in function or appearance, but not in origin or development; cf. *homologous*, def. 1.

**analogue** (an'ah-log) 1. a part or organ having the same function as another, but of a different evolutionary origin; cf. *homologue* (def. 1). 2. a chemical compound with a structure similar to that of another but differing from it in respect to a certain component; it may have a similar or opposite action metabolically. Cf. *homologue* (def. 2). **base a.**, an analogue of a purine or pyrimidine base, as aminopurine. **homologous a.**, a part that is similar to another in both function and structure. **metabolic a.**, a closely similar compound which tends to replace an essential metabolite. **substrate a.**, a substance with a structure similar to the natural substrate of an enzyme and which, because of this similarity, inhibits the action of the enzyme, as in competitive inhibition.

**analogy** (ah-nal'o-je) [Gr. *analogia* equality of ratios, proportion] the quality of being analogous; resemblance or similarity in function or appearance, but not in origin or development.

**anaphalipoproteinemia** (an-al'fah-lip'o-pro'te-in-e'me-ah) Tangier disease.

**analysand** (ah-nal'i-sand) one who is being psychoanalyzed.

**analysis** (ah-nal'i-sis), pl. *analyses* [ana- + Gr. *lysis* dissolution] 1. separation into component parts or elements; the act of determining the component parts of a substance. 2. psychoanalysis. **activation a.**, a quantitative determination of the presence of certain types of nuclei in a sample by transmuting them into radioactive nuclei and analyzing the emanating radiation. **antigenic a.**, the determination of the components of the antigenic mosaic of a bacterial species. **bite a.**, occlusal a. **blood gas a.**, the determination of oxygen and carbon dioxide concentrations and the pH of the blood by laboratory tests; the following measurements may be made:  $PO_2$ , partial pressure of oxygen in arterial blood;  $PCO_2$ , partial pressure of carbon dioxide in arterial blood;  $SO_2$ , percent saturation of hemoglobin with oxygen in arterial blood; the total  $CO_2$  content of (venous) plasma; and the pH. **bradycardiac a.**, cineradiographic study of motor activity. **cephalometric a.**, a study or analysis of the skeletal and dental relationships used in orthodontic case analysis, as seen in cephalograms. **character a.**, the systematic psychotherapeutic investigation or analysis of the personality traits or defenses of an individual. **chromatographic a.**, chromatography. **colorimetric a.**, analysis by means of the various color tests. **densimetric a.**, analysis by ascertaining the specific gravity of a solution and estimating the amount of matter dissolved. **distributive a.**, psychobiologic treatment by the

directed study and interpretation of the patient's present and past behavior. **Downs' a.**, a series of cephalometric criteria developed by Downs as an aid in orthodontic diagnosis. **ego a.**, the intensive therapeutic study and analysis of the ways in which the ego resolves or attempts to deal with intrapsychic conflicts. **end-group a.**, evaluation of the degree of linearity and branching of polysaccharide by determination of the number of end groups; determination of the amino- and carboxyl-terminal amino acids of a protein permitting an evaluation of the number of peptide chains per molecule as well as the state of purity of the protein. **existential a.**, existential psychoanalysis. **gasometric a.**, the measurement of the different components of a gaseous mixture. **gravimetric a.**, quantitative a. **group a.**, intensive psychotherapeutic analysis in which two or more patients actively participate. **occlusal a.**, a study of the relations of the teeth in one jaw to those in the opposite jaw as units; called also *bite a.* **organic a.**, the analysis of animal and vegetable tissues. **polariscopic a.**, analysis by means of the polariscope. **proximate a.**, the determination of the simpler constituents of a substance. **qualitative a.**, qualitative a., the determination of the nature of the constituents of a compound or a mixture of compounds. **quantitative a.**, quantitative a., the determination of the proportionate quantities of the constituents of a compound. **radiochemical a.**, direct or indirect identification or determination of the content of specific elements in a substance through measurement of the disintegration rates of radionuclides. **spectroscopic a.**, spectrum a., analysis by means of determining the wave length(s) at which electromagnetic energy is absorbed by a sample. **tetrad a.**, the analysis of crossing over by studying all the tetrads arising from the meiotic divisions of a single primary gametocyte. **transactional a.**, a type of psychotherapy involving an understanding of the interpersonal interchanges between the components of the personalities of the participants (individuals or members of a group). **ultimate a.**, the determination of the ultimate elements of a compound. **vector a.**, analysis of a moving force to determine both its magnitude and its direction, e.g., analysis of the scalar electrocardiogram to determine the magnitude and direction of the electromotive force for one complete cycle of the heart. **volumetric a.**, quantitative analysis by measuring volumes of liquids.

**analysor** (an'ah-li'zor) analyzer.

**anolyte** (an'ah-lit) a substance undergoing analysis.

**analytic** (an'ah-lit'ik) pertaining to analysis.

**analyzer** (an'ah-li'zer) 1. a Nicol prism attached to a polarizing apparatus which extinguishes the ray of light polarized by the polarizer. 2. Pavlov's name for a specialized part of the nervous system which controls the reactions of the organism to changing external conditions. 3. a nervous receptor together with its central connections, by means of which sensitivity to stimulations is differentiated. **amino acid a.**, an analytical instrument that separates, identifies, and measures quantities of amino acids and related compounds. **amino acid sequence a.**, an instrument for determining protein components in plasma, useful in blood-lipid evaluation. **blood gas a.**, an instrument for measuring partial pressures of oxygen, carbon dioxide, carbon monoxide, and nitrogen in blood. **breath a.**, an instrument for determining the volume and composition of respired gases; some types are specifically designed for detecting alcohol in the breath. **image a.**, an instrument that counts, measures and classifies cells and images viewed on microscopes, photographs, transparencies, etc. **oxygen gas a.**, an instrument for measuring the oxygen content of a gaseous mixture, or dissolved oxygen in a liquid, or saturation of blood hemoglobin with  $O_2$  or partial pressure of  $O_2$  in blood. **voice a.**, an electronic instrument for printing out waveforms corresponding to vocal characteristics, as an aid in identifying voice and speech problems or a particular speaker.

**Aname** (an'ah-me) a genus comprising the venomous "bird spiders" of the family Theraphosidae.

**Anamirta cocculus** L. Wight & Arn. (Menispermaceae) (an'ah-mer'tah kok'u-lus) a species of East Indian woody vines whose dried berries or fruit, cocculus indicus, yield picrotoxin. Called also *A. paniculata*.

**anamirtin** (an'ah-mer'tin) an oily glyceride,  $C_{18}H_{34}O_{10}$ , from the dried berries or fruit of *Anamirta cocculus*.

**anamnesis** (an'am-ne'sis) [Gr. *anamnēsis* a recalling] 1. the faculty of memory. 2. the collected data concerning a patient, his family, previous environment, and experiences, including any abnormal sensations, moods, or acts observed by the patient himself or by others, with the dates of their appearance and duration, as well as any results of treatment. 3. in immunology, the faculty of immunological memory as exemplified by events in the secondary or anamnestic immune response.

**anamnestic** (an'am-nes'tik) pertaining to anamnesis. See also under response.

**Anamniota** (an'am-ne-o'tah) [an priv. + Gr. *amnion*] a major group of vertebrates comprising those which develop no amnion, including fishes and amphibians; opposed to Amniota.

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